

WHAT IS CLAIMED IS:

1. A method of propagating uterine bud cells in culture, comprising
 - (a) culturing a UB in vitro under conditions that induce the UB to undergo branching morphogenesis to generate a population of UBs comprising tubular branches; and
 - (b) subdividing the UB population; and
 - (c) resuspending each subpopulation in culture media and repeating (a) and (b).
2. The method of claim 1, wherein the conditions comprise culturing the UB in the presence of BSN-CM, FGF1, and GDNF.
3. A method for in vitro culturing and propagating ureteric bud tissue, comprising:
 - isolating ureteric bud tissue from mesenchyme tissue obtained from embryonic kidney rudiments;
 - culturing the isolated ureteric bud tissue in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof for a sufficient time and under sufficient conditions to produce tubular branches within the biocompatible matrix;
 - separating the plurality of branch tips to generate bud fragments; and
 - culturing each of the bud fragments in a biocompatible matrix with a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof.
4. The method of claim 3, wherein the culture medium further comprises a glial cell line derived neurotrophic factor (GDNF) or functional equivalent thereof.
5. The method of claim 3, wherein the culture medium further comprises FGF1 or a functional equivalent thereof.
6. The method of claim 3, wherein the biocompatible matrix comprises a material selected from the group consisting of a cotton, a collagen, a polyglycolic acid, a cat gut suture, a cellulose, a gelatin, a dextran, a polyamide, a polyester, a polystyrene, a

polypropylene, a polyacrylate, a polyvinyl, a polycarbonate, a polytetrafluorethylene, a nitrocellulose compound, and a Matrigel.

7. The method of claim 6, wherein the material is treated to contain proteoglycans, Type I collagen, Type IV collagen, laminin, proteoglycans, fibronectin, or combinations thereof.

8. A method for growing renal tubule cells in vitro, comprising culturing kidney cells in a growth medium comprising pleiotrophin and/or heregulin in an amount effective for achieving tubulogenesis.

9. The method of claim 8, wherein the growth medium further comprises a factor selected from the group consisting of FGF1, GDNF, and a combination thereof.

10. The method of claim 8, wherein the growth medium comprises a factor selected from the group consisting of Type I collagen, Type IV collagen, laminin, proteoglycans, fibronectin, and combinations thereof.

11. A method for stimulating epithelial organogenesis, comprising:
contacting an epithelial tissue with an effective amount of a composition comprising one or more mesenchymally derived growth factor(s) secreted by mesenchymal tissue in culture; and
culturing the epithelial tissue and the composition for a sufficient period of time and under conditions to allow the tissue and the composition to interact, wherein the composition stimulates epithelial organogenesis.

12. The method of claim 11, wherein the composition comprises a factor selected from the group consisting of pleiotrophin and/or heregulin, GDNF, FGF1, and any combination thereof.

13. The method of claim 11, wherein the composition comprises cell culture medium obtained from BSN cells.
14. The method of claim 11, wherein the epithelial tissue is selected from the group consisting of kidney tissue, lung tissue, prostate tissue, neural tissue, glandular tissue, hepatic tissue, and salivary gland tissue.
15. An epithelial tissue obtained by the method of claim 11.
16. A method of stimulating branching morphogenesis in an epithelial tissue comprising contacting the epithelial tissue with a composition comprising pleiotrophin and/or heregulin.
17. The method of claim 16, wherein the epithelial tissue is selected from the group consisting of kidney tissue, lung tissue, prostate tissue, neural tissue, glandular tissue, hepatic tissue, and salivary gland tissue.
18. The method of claim 16, wherein the tissue is contacted in vitro.
19. The method of claim 16, wherein the tissue is contacted in vivo.
20. The method of claim 16, wherein the tissue is contacted ex vivo.
21. A method for in vitro tissue engineering of a functional mammalian epithelial tissue, organ or a fragment thereof comprising:
 - culturing and propagating embryonic epithelial explant, tissues, and/or cells by isolating the explant, tissue, and/or cells and growing the explant, tissue, and/or cells in a culture medium comprising pleiotrophin and/or heregulin, permitting the culture to form multiple branches, dissecting out individual tips of the branches;
 - reculturing the branch tips in the culture medium comprising pleiotrophins;

combining the branch tips with embryonic or fetal mesenchymal tissue and/or cells, in the presence of the mixture of a culture medium in or on a biocompatible substrate; and culturing the combination in culture medium conditions suitable for tissue growth and tubulogenesis.

22. A method for stimulating branching morphogenesis in a kidney cell culture, comprising:

contacting the kidney cell culture with an effective amount of a composition comprising one or more mesenchymally derived growth factor(s) secreted by a mesenchyme tissue in culture; and

culturing the kidney cell culture and the composition for a sufficient period of time and under conditions to allow the cells and the composition to interact, wherein the composition stimulates branching tubular morphogenesis.

23. The method of claim 22, wherein the kidney cell culture comprises uterine bud cells.

24. The method of claim 22, wherein the mesenchyme tissue is metanephric mesenchyme.

25. The method of claim 22, wherein the mesenchymally derived growth factor is secreted by metanephric mesenchyme tissue in culture.

26. The method of claim 25, wherein the mesenchymally derived growth factor is from BSN cell conditioned medium.

27. The method of claim 22, wherein the mesenchymally derived growth factor is a heparin-binding polypeptide.

28. The method of claim 27, wherein the heparin-binding polypeptide is a pleiotrophin and/or heregulin polypeptide or an active fragment thereof.

29. The method of claim 22, wherein the composition comprises a conditioned medium obtained from BSN cells in culture.

30. The method of claim 22, wherein the composition comprises pleiotrophin and/or heregulin.

31. The method of claim 30, wherein the pleiotrophin and/or heregulin is obtained from culture medium of a metanephric mesenchymal culture.

32. The method of claim 30, wherein the pleiotrophin and/or heregulin is a recombinant pleiotrophin and/or heregulin.

33. The method of claim 32, wherein the recombinant pleiotrophin and/or heregulin comprises an active fragment of pleiotrophin and/or heregulin.

34. The method of claim 32, wherein the recombinant pleiotrophin and/or heregulin is a peptidomimetic pleiotrophin and/or heregulin.

35. The method of claim 22, wherein the composition comprises a pleiotrophin and/or heregulin analogue.

36. The method of claim 22, wherein the composition comprises a synthetic pleiotrophin and/or heregulin analogue.

37. The method of claim 30, wherein the composition further comprises GDNF and/or FGF1.

38. The method of claim 22, wherein the kidney cell culture comprises uteric bud cells and metanephric mesenchyme cells.

39. A kidney tissue obtained by the method of claim 22.

40. A method of in vitro culturing and propagating metanephric mesenchyme tissue, comprising:

isolating mesenchyme tissue at the time of induction;

culturing the mesenchymal tissue in a composition comprising serum, nutrient rich medium, and mesenchymal and/or ureteric bud cell conditioned medium; and

partitioning the cultured mesenchyme into multiple pieces and growing each piece separately in culture.

41. The method of claim 40, wherein the method further comprises subjecting the cultured mesenchyme to nutrient deprivation and/or addition of vasculogenic growth factors in order to induce vasculogenesis.

42. The method of claim 40, wherein the vasculogenic growth factor is pleiotrophin and/or heregulin.

43. A method for in vitro engineering and constructing a mammalian kidney, comprising:

separating ureteric bud (UB) tissue from mesenchyme tissue obtained from an embryonic kidney rudiment;

culturing the isolated ureteric bud tissue in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof for a sufficient time and under sufficient conditions to produce tubular branches within the biocompatible matrix;

separating the tubular branches to obtain a plurality of bud fragments;

culturing each of the bud fragments in a biocompatible matrix with a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof to generate a plurality of tissues comprising tubular branches;

combining the plurality of tissues comprising tubular branches with metanephric mesenchyme (MM) tissue in the presence of nutrient medium comprising pleiotrophin and/or heregulin; and

culturing the UB and MM under conditions sufficient to cause the MM to differentiate and form nephron structures thereby forming a kidney.

44. The method of claim 43, wherein the propagated UB tissue comprises epithelial cells.

45. The method of claim 43, wherein the culture medium further comprises a glial cell line derived neurotrophic factor (GDNF) or functional equivalent thereof.

46. The method of claim 43, wherein the culture medium further comprises FGF1 or a functional equivalent thereof.

47. The method of claim 43, wherein the biocompatible matrix comprises a material selected from the group consisting of a cotton, a collagen, a polyglycolic acid, a cat gut suture, a cellulose, a gelatin, a dextran, a polyamide, a polyester, a polystyrene, a polypropylene, a polyacrylate, a polyvinyl, a polycarbonate, a polytetrafluorethylene, a nitrocellulose compound, and a Matrigel.

48. The method of claim 43, wherein the material is treated to contain proteoglycans.

49. A tissue engineered kidney produced by the method of claim 43.

50. A functional mammalian kidney engineered and constructed in vitro, comprising:

a ureteric bud (UB) tissue propagated in culture in the presence of a composition comprising pleiotrophin and/or heregulin to produce a functioning tubular structures; and

a metanephric mesenchyme (MM) tissue propagated from cultured embryonic mesenchymal tissue fragments or cells to produce functioning nephrons wherein the ureteric bud tissue and the metanephric mesenchyme are co-cultured and wherein the uteric bud tissue induces the metanephric mesenchyme to form nephrons, thereby forming a functional mammalian kidney.

51. The functional kidney of claim 50, wherein the UB and/or MM are genetically engineered to produce a product of interest.

52. The functional kidney of claim 51, wherein the product of interest is a therapeutic or diagnostic polypeptide.

53. The functional kidney of claim 50, wherein the UB tissue is propagated in combination with a biocompatible matrix material.

54. A genetically engineered mammalian kidney produced by a method comprising:

culturing a population of cells comprising ureteric bud (UB) cells in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof for a sufficient time and under sufficient conditions to produce tubular branches within the biocompatible matrix, and wherein at least one ureteric bud cell of the population of cells is transfected with an exogenous polynucleotide such that the exogenous polynucleotide expresses a product;

separating the tubular branches to obtain a plurality of bud fragments;

culturing each of the bud fragments in a biocompatible matrix with a culture medium comprising pleiotrophin and/or heregulin or an active fragment thereof to generate a plurality of tissues comprising tubular branches;

combining the plurality of tissues comprising tubular branches with metanephric mesenchyme (MM) tissue in the presence of nutrient medium comprising pleiotrophin and/or heregulin; and

culturing the UB and MM under conditions sufficient to cause the MM to differentiate and form nephron structures thereby forming a kidney.

55. The genetically engineered mammalian kidney of claim 54, wherein the population of cells are substantially homogenous for UBs.

56. The genetically engineered mammalian kidney of claim 54, wherein the population of cells comprise cells selected from the group consisting of fibroblasts, endothelial cells, mesenchymal stem cells, hematopoietic stem cells, circulating stem cells, glomerular cells, mesangial cells, interstitial cells, tubular cell, endothelial cells, and any combination thereof.

57. A method of treating a subject suffering from kidney failure comprising transplanting a tissue engineered kidney of claim 54 into the subject.

58. A method of transplantation comprising transplanting the tissue of any one of claims 15, 39, 49, or 54 into a subject.

59. The method of claim 58, wherein the tissue is implanted into a subject for the purpose of regeneration.

60. The method of claim 58, wherein the tissue is implanted into a subject due to ischemic or toxic insult.

61. The method of claim 58, wherein the tissue is implanted into a subject for the purpose of protection and growth of the tissue.

62. A method for treating acute renal failure comprising administering to a subject suffering from ARF with a pharmaceutically effective amount of a composition comprising pleiotrophin and/or heregulin such that a symptom of ARF is ameliorated.

- 63. The method of claim 62, wherein the compositions further comprises heregulin.
- 64. The method of claim 62, wherein the composition further comprises GDNF.
- 65. The method of claim 62, wherein the composition further comprises FGF1.
- 66. The method of claim 62, wherein the administering is selected from the group consisting of intravenous, intramuscular, intradermal, and subcutaneous.
- 67. A renal tubule cell produced by culturing ureteric bud cells in a culture medium comprising pleiotrophin and/or heregulin in an amount effective for achieving tubulogenesis.